

REMARKS

Claims 12, 14, 16-18, and 20-37 were pending. The Examiner rejected claims 12, 14, 17, 18, 20, 22-27, 29-34, 36, and 37, and withdrew claims 16, 21, 28, and 35 as drawn to non-elected subject matter. Applicants have herein amended claims 12, 16, and 17 to recite the four compounds that correspond to Compounds 1-4 in the Examples, and have amended claims 18 and 20 to alter the dependency and to limit the claims to Compound 1 as set forth in the Examples, or a pharmaceutically acceptable salt thereof. No new matter has been added.

In light of the amendments and the remarks herein, Applicants respectfully request reconsideration and allowance of the pending claims.

Withdrawal of Claims

The Examiner again withdrew claims 16, 21, 28, and 35 as drawn to non-elected subject matter, but provided no explanation of the withdrawal or comments as to Applicants' prior comments on the withdrawal. On page 2 of the Office Action, the Examiner also noted that rejections that were not reiterated from the previous Office Actions were withdrawn. Applicants respectfully disagree with the withdrawal, reiterate that Applicants traversed this withdrawal in the last Response, and request clarification of the status of the claims. The Restriction Requirement dated July 17, 2007 stated that Group II included original claims 12-17, drawn to a "method of treatment" using a c-Kit kinase inhibitor. The Restriction Requirement went on to indicate that if Group II was elected, a species of cancer for claims 13-14 (*see* page 6 of the Restriction Requirement) was required. Original claim 16 was directed to a method of treating mastocytosis, allergy, or asthma, and was included in the claims indicated by the Examiner to fall in Group II (*i.e.*, claims 12-17). Applicants subsequently elected Group II, and indicated that claims 12-15 and 17 of Group II read on the species of small cell lung cancer. In subsequent Office Actions, the Examiner did not withdraw claim 16 as drawn to non-elected subject matter or issue another Restriction Requirement. Applicants respectfully assert that while claim 16 does not read on the elected species of small cell lung cancer, it does fall within the elected Group II, drawn to a method of treatment using a c-Kit kinase inhibitor. Applicants respectfully request

that the Examiner reconsider the withdrawal of claims 16, 21, 28, and 35, and clarify the status of these claims.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 12, 14, 17-18, 20, 22-27, 29-34, and 36-37 as failing to enable the entirety of the Markush-type Formula I for the utility asserted. For example, the Examiner indicated that the pharmaceutical arts are unpredictable and require each embodiment to be individually assessed for physiological activity. In reviewing the *In re Wands* factors, the Examiner acknowledged that the level of skill in the art was high, and with respect to the term “correlation”, stated that “if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.” The Examiner went on to state that *in vitro* assays or cell-cultured based assays lack correlations with clinical efficacy, allowing not a “single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability.” The Examiner cited passages from the Freshney, Dermer, and Gura references, noting in particular that of the “thousands” of drugs that have shown activity in either cell or animal models, “*only 39 have ... won approval from the FDA*” as chemotherapeutics (emphasis added).

With respect to the Applicants’ data, the Examiner acknowledged that Compounds 1-4 inhibited cell proliferation stimulated by SCF and that these compounds were *considered* to possess c-kit kinase inhibitory activity *in vitro* (Examiner’s emphasis). The Examiner went on to state that while the specification provided an example of inhibiting *in vivo* phosphorylation using the elected compound (Compound 1), the specification appeared to be silent on any correlation between the *in vitro* testing of compounds 2-4 and the rest of the scope of Formula I with *in vivo* success. The Examiner then concluded that the *in vitro* examples did not constitute working examples, citing no case law or guidance to support such a position.

Applicants respectfully disagree. The Examiner has not established a *prima facie* case of lack of enablement, particularly with respect to the claims as currently amended. The test of

enablement is whether the specification teaches one skilled in the art how to make and use the full scope of the claimed invention without “undue” experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Importantly, “a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken in compliance with the enablement requirement of the first paragraph unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” *In re Marzocchi*, 439 F.2d 220, 222-223 (CCPA 1971) (emphasis in the original). The Examiner bears the burden of “providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.” *In re Wright* at 1561. The Examiner has not met that burden in the present case.

The presently amended claims recite the use of four particular compounds in the claimed methods. Methods for making these compounds, as well as their structures and chemical names, were clearly described in the specification. These four compounds were examined for their effects on SCF-induced proliferation of a small cell lung cancer cell line H-526, which expresses c-Kit kinase; the experimental protocol for such an assay was set forth clearly in Example 1. Paragraph [0005] notes that c-Kit kinase binds to SCF, causing dimerization of c-Kit kinase and activation of its kinase activity. Abnormal activation of c-Kit kinase generates a proliferation signal in certain types of cancer cells, which is regarded as the cause of malignant transformation; *see* [0006]. Based on the results of the inhibition of SCF cell proliferation assay, these four compounds were considered to possess c-Kit kinase inhibitor activity. The four compounds' IC₅₀ (nM) values were in fact favorable as compared to ST1571 (Gleevec), which is known in the prior art as a c-Kit kinase inhibitor, and KRN633, which has also been reported in the prior art to possess c-Kit kinase inhibitor activity (*see* paragraph [0022]). Accordingly, the Examiner's assertion that the Specification was *silent* as to any correlation between the *in vitro* testing and *in vivo* inhibition of phosphorylation or therapeutic activity is incorrect, as two art-recognized c-Kit kinase inhibitors, one of which is an FDA-approved chemotherapeutic (Gleevec), were evaluated in the Specification using the same assay as the presently claimed four

compounds. Moreover, Applicants submit herewith two additional references, published before the priority date of the present application, that demonstrate a correlation between inhibition of SCF-stimulated cell proliferation and c-Kit inhibition and anti-cancer activity.¹ These references demonstrate that the H526 assay employed in the present specification is an art-recognized assay that supports a correlation between inhibition of SCF-stimulated cellular proliferation and c-Kit inhibition and consequent anti-cancer effect. Here, the art recognized that inhibition of H526 cell proliferation correlated with c-Kit inhibition and consequent anti-cancer effect, and the Examiner has provided no evidence that such a correlation is not true. A person having ordinary skill in the art would thus recognize Applicants' *in vitro* working examples as enabling methods of inhibiting c-Kit mediated phosphorylation and malignant transformation *in vivo*. See *In re Brana*, 51 F.3d at 1567-68 (finding statistically significant data obtained from established mouse tumor models sufficient to satisfy § 112, first paragraph). Thus, the Examiner's argument that Applicants have provided insufficient *in vivo* evidence to enable a person having ordinary skill in the art to practice the claimed invention is unwarranted.

While the Examiner asserts that Applicants have failed to meet the enablement standard according to the factors laid out in *In re Wands*, the Examiner apparently seeks data that would be obtained only from full-blown clinical trials. Specifically, the Examiner notes that due to the alleged unpredictability of the art, the quantity of experimentation necessary to practice the claimed methods with any predictability of success is too great for patentability. Applicants assert that such a conclusive determination of clinical, therapeutic, or diagnostic efficacy is not required for patentability - even for therapeutic cancer methods. Applicants need not await results of clinical trials to claim methods of treatment as presently recited. The courts have consistently held that the Examiner's standard is not the proper level of inquiry when assessing enablement under Title 35. As recently held by the Federal Circuit, "providing proof sufficient to justify conducting *in vivo* procedures on humans, while useful, is not a test of patentability." *PharmaStem Therapeutics, Inc. v. Viacell, Inc.*, 2007 WL 1964863 at *20 (Fed. Cir. 2007). The patent applicant need only produce experimental proof that procedures carried out in other

¹ See Krystal *et al.*, Clinical Cancer Research, Vol. 6:3319-3326 (2000) and Krystal *et al.*, Cancer Research, Vol. 61:3660-3668 (2001).

systems may be extrapolated for use in humans. *Id. See also In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995) (holding that applicants need not produce data that could only be obtained from Phase II clinical trials to satisfy § 112, first paragraph); *Cross v. Iizuka*, 753 F.2d 1040, 1051 (Fed. Cir. 1985) (holding that successful *in vitro* testing for a particular pharmacological activity may establish a significant probability that *in vivo* testing would be successful). Indeed, the Examiner's assertion that the present Specification's *in vitro* examples did not constitute "working examples" seems to directly contradict the prevailing case law, particularly given the fact that the Examiner has not provided any case law to support such a position. Moreover, the Examiner's own argument that "thousands of drugs show activity in either cell or animal models" and that only 39 have actually "won approval from the FDA" actually supports Applicants' assertions that a skilled artisan *may in fact draw clinical correlations* from cell and animal models, that such model systems are *indeed useful* for developing therapeutic cancer agents, and that the Examiner is using an improper standard for enablement (*i.e.*, FDA approval). Accordingly, given all of the above, Applicants respectfully assert that it would not require undue experimentation for one having ordinary skill in the art to practice the claimed invention. Withdrawal of the rejections is respectfully requested.

CONCLUSION

Applicants respectfully assert that all claims are in condition for allowance, which action is hereby requested. The Examiner is invited to telephone the undersigned attorney if such would expedite prosecution.

No fee is believed due. Please apply any other charges or credits to deposit account 06-1050.

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Respectfully submitted,

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/Teresa A. Lavoie/

Teresa A. Lavoie, Ph.D.
Reg. No. 42,782

Fish & Richardson P.C.
3200 RBC Plaza
60 South Sixth Street
Minneapolis, Minnesota 55402
Telephone: (612) 335-5070
Facsimile: (877) 769-7945